FROM THE ANALYST'S COUCH

Monoclonal antibodies market

Janice Reichert and Alex Pavlou

'Little Beaver', designed by Frank O'Gehry, from Vitra.com (photographer Hans Hansen)

Following the success of recombinant proteins, therapeutic monoclonal antibodies (mAbs) represent the second wave of innovation created by the biotechnology industry during the past twenty years. Between 2001 and 2002, the value of the global therapeutic mAb market grew by 37% to US $5.4 billion. Chimeric mAbs were the undisputed leaders, with 43% growth and US $3.8 billion in sales, followed by humanized mAbs with more than US $1.4 billion in sales and growth of 29%. The current global clinical antibody pipeline, which comprises 132 products in development and is dominated by humanized (42%) and fully human (28%) mAbs, is poised to deliver as many as 16 new products between 2004 and 2008. As a result of growth in existing markets for mAb therapeutics, and the opening of new ones, the global market is projected to increase to US $16.7 billion in 2008.

mAbs approved for marketing

To date, 17 therapeutic mAbs, comprising four different types, have been approved by the US FDA: three murine, five chimeric, eight humanized and one human. Nine of the seventeen mAbs have also been approved in the European Union (EU). All of these products were approved in the United States first, though all were approved in the EU within two years of the US approval date. Mean approval times for mAbs are faster in the United States compared with the EU because the FDA has given priority review designation to a majority of the marketing applications. Of the approved products, the best-seller is Johnson & Johnson/Schering-Plough's infliximab (Remicade), with sales of US $1.6 billion, representing 30.5% of the total market sales in 2002. This product was also the fastest-growing product in 2002, with sales increasing by 84%.

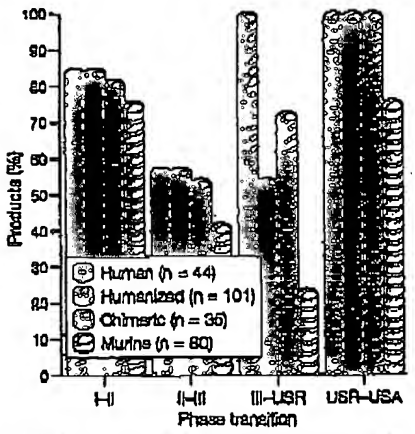

Figure 1 | Phase transition probabilities* for four types of therapeutic mAbs. *Phase transition probabilities were calculated as follows: the number of products that completed a given phase (for example, Phase I) and entered the next (for example, Phase II) was divided by the difference between the number of products that entered the phase and those that were still in the phase at the time of the calculation. Clinical studies for human antibodies initiated during 1994 to 2003. Source: Tufts Center for the Study of Drug Development. USA, US approval; USR, US review.

Advancing to the next phase

Although many products might start on the path to approval, not all will complete the convoluted process. In our analysis, probabilities of product advancement from the start of clinical development through US approval were calculated on the basis of current development status of 260 products identified as either murine, chimeric, humanized or human mAbs (FIG. 1). Murine mAbs had the lowest transition probabilities at each phase. The chimeric, humanized and human products had similar Phase I to II and Phase II to III transition probabilities, but the probabilities diverged at the Phase III to US review transition. For the vast majority of mAb products, if the FDA filed the marketing application, then the product ultimately received approval.

Measure of success

Approval success rates are a measure of the likelihood of receiving marketing approval for a product that enters clinical testing. The range of overall approval success for the four types of mAbs was large. To date, the murine products have been least successful (4.5%), whereas the chimeric mAbs have been most successful (26%). The approval success rates for the humanized (18%) and human (14%) mAbs were in the middle of the range. The majority of the humanized and human mAbs are still in clinical development, so the approval success rates might change as the fate of more products is determined. Additional variation in the success rates was observed when the mAbs were categorized by both type and therapeutic category. For example, the success rates for antineoplastic and immunological chimeric mAbs were 29%, whereas humanized antineoplastic and immunological mAbs had a 25% and 17% success rate, respectively.

Waves of the future

Looking toward the future, we anticipate two major approval waves during the next five years. The first will occur between 2004 and 2006, with humanized antibodies comprising the largest number of approvals, whereas the second will occur between 2007 and 2008, and be dominated by human antibody products. Of particular interest, Osidem (ImmunoDesigned Molecules), a combination of a bispecific mAb and macrophage-activated killer cells, and two radiolabelled antibodies might reach the market by 2008. One product produced using a novel engineering approach, Celltech's fragmented antibody CDP-870, is expected to launch in 2006.

A growing market

Although growth will rely on the rise of humanized and human antibodies, chimerics, led by infliximab and rituximab (Rituxan; Genentech), will dominate with a 43% market share in 2008. Humanized antibodies will follow, with sales forecast to reach US $5.2 billion, or a 31% market share by 2008. In addition, fully human antibodies with 2008 sales of US $1.9 billion, will capture 11% of the market in 2008.

Two therapeutic categories — oncology and arthritis, immune and inflammatory disorders (AIID) — will likely be the commercial and research focus during the next four years. With the recent approvals of cetuximab (Erbitux; Imclone Systems) and bevacizumab (Avastin; Genentech), oncology will be the leading income earner, with forecast sales of US $7.2 billion in 2008, representing a 43% market share. Meanwhile, AIID sales will almost quadruple from US $1.7 billion to $6.7 billion in 2008, or a 40% market share. In addition, the industry might see approvals in new areas such as the 2005 launch of the humanized antibody natalizumab (Antegren; Biogen IDEC/Elan) for the treatment of multiple sclerosis.

MONOCLONAL ANTIBODIES MARKET | MARKET INDICATORS

▶ The antibody-focused biotechnology industry has garnered US marketing approval for 13 therapeutic mAbs during the past six years (TABLE 1). During the next five years, the industry has the potential to double the number of approved mAbs, and can anticipate a tripling of the global market for mAb products (see FIGS 2,3). To achieve this result, the industry needs to continue to evolve towards technology integration and market expansion. Success will depend on strategies targeting shorter development times, higher success rates, innovative molecular engineering, robust intellectual property protection and the development of cost-effective manufacturing.

Janice Reichert, Ph.D., is Senior Research Fellow at Tufts Center for the Study of Drug Development, 192 South Street, Suite 550, Boston, Massachusetts 02111, USA. Alex Pavlou, Ph.D., heads Biotechnology Analysis at Datamonitor Healthcare, 108–110 Finchley Road, Charles House, London, NW3 5JJ, UK
e-mails janice.reichert@tufts.edu; apavlou@datamonitor.com

doi:10.1038/nrd1386

1. Reichert, J. M. Trends in development and approval times for new therapeutics in the United States. *Nature Rev. Drug Discov.* 2, 695–702 (2003).

Online links

FURTHER INFORMATION
US Food and Drug Administration: http://www.fda.gov
European Agency for the Evaluation of Medicinal Products: http://www.emea.eu.int
Access to this interactive links box is free online.

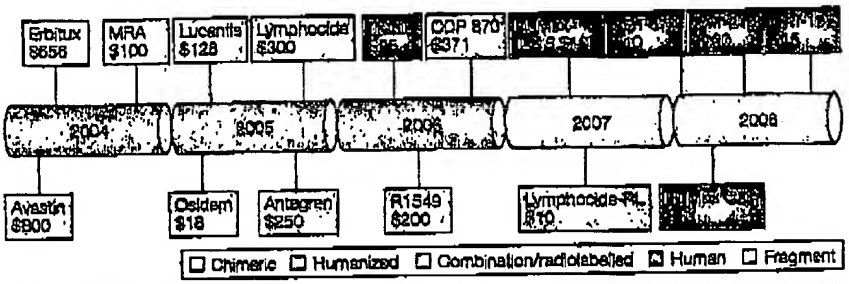

Figure 2 | New product approval trajectories in terms of technological exposure and sales potential in 2008. Sixteen new antibodies are expected to reach the market over the next four years. Amounts in US $ millions. Source: Datamonitor. IL, interleukin; MRA, humanized anti-human IL-6 receptor monoclonal antibody.

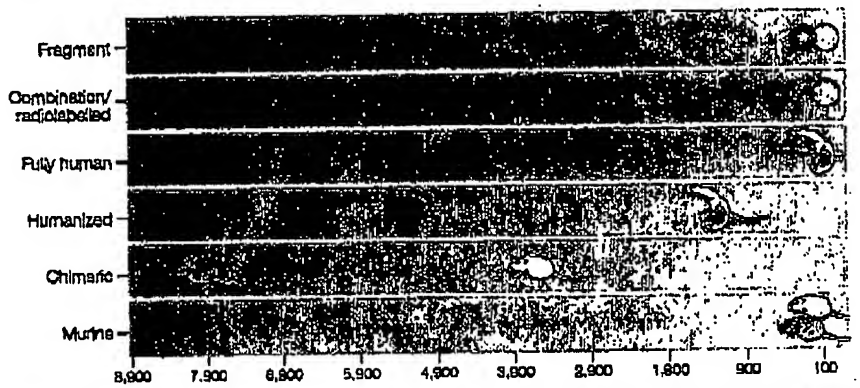

Figure 3 | Comparison of therapeutic mAb sales trajectories in 2002 (yellow) and 2008 (blue) in terms of technological focus. Despite the undisputed leadership of chimeric mAbs, the contribution of humanized and fully human products to total market size will significantly rise. Source: Datamonitor.

Table 1 | Therapeutic mAbs approved in the United States and European Union

Sponsor company	Generic name	US trade name	mAb type	Therapeutic category	US approval date	EU* approval date
Johnson & Johnson	Muromonab-CD3	Orthoclone OKT3	Murine	Immunological‡	19.06.1986	NA
Centocor	Abciximab	ReoPro	Chimeric	Hemostasis	22.12.1994	NA
Biogen IDEC	Rituximab	Rituxan	Chimeric	Antineoplastic	26.11.1997	02.06.1998
Protein Design Labs	Daclizumab	Zenapax	Humanized	Immunological	10.12.1997	26.02.1999
Novartis	Basiliximab	Simulect	Chimeric	Immunological	12.05.1998	09.10.1998
MedImmune	Palivizumab	Synagis	Humanized	Anti-infective	19.06.1998	13.08.1999
Centocor	Infliximab	Remicade	Chimeric	Immunological	24.08.1998	13.08.1999
Genentech	Trastuzumab	Herceptin	Humanized	Antineoplastic	25.09.1998	28.08.2000
Wyeth	Gemtuzumab ozogamicin	Mylotarg	Humanized	Antineoplastic	17.05.2000	NA
Millennium/ILEX	Alemtuzumab	Campath	Humanized	Antineoplastic	07.05.2001	08.07.2001
Biogen IDEC	Ibritumomab tiuxetan	Zevalin	Murine	Antineoplastic	19.02.2002	16.01.2004
Abbott	Adalimumab	Humira	Human	Immunological	31.12.2002	08.09.2003
Genentech	Omalizumab	Xolair	Humanized	Immunological	20.06.2003	NA
Corixa	Tositumomab-I131	BEXXAR	Murine	Antineoplastic	27.06.2003	NA
Genentech	Efalizumab	Raptiva	Humanized	Immunological	27.10.2003	NA
Imclone Systems	Cetuximab	Erbitux	Chimeric	Antineoplastic	12.02.2004	NA
Genentech	Bevacizumab	Avastin	Humanized	Antineoplastic	26.02.2004	NA

*Approved using EU centralized procedure. ‡Includes arthritis, immune and inflammatory disorders and prevention/reversal of transplant rejection; NA, not approved.
Source: Tufts Center for the Study of Drug Development.